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Treatment of gonorrhoea and susceptibility to antimicrobials of PPNG and non-PPNG strains in Jamaica

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SUMMARY Of 1400 patients in Jamaica screened for uncomplicated gonorrhoea, 54% (753 patients) were culture positive. Of the 459 patients who complied with the terms of the study, 97% (211/218) of those treated with aqueous procaine penicillin G were cured compared with 94% (227/241) of those treated with ampicillin. Penicillinase producing *Neisseria gonorrhoeae* (PPNG) strains were identified for the first time during the study, and 10 patients infected with PPNG strains (two treated with penicillin, eight with ampicillin) contributed to the 21 treatment failures. The in vitro susceptibility of eight antimicrobial agents for 629 non-PPNG and 20 PPNG strains was estimated. Of the non-PPNG isolates, 8% had an MIC of 1 mg/l or more of penicillin, 11% were resistant to this concentration of ampicillin, 32% to tetracycline, and under 1% to the same concentration of cefuroxime and erythromycin. Fewer than 2% of the isolates were resistant to 2 mg/l or more thiamphenicol, and all isolates were susceptible to spectinomycin and trimethoprim-sulphamethoxazole (at a ratio of 1:19). Significantly more strains from the 21 treatment failures were resistant to penicillin (52%) or ampicillin (62%) compared with 7% strains resistant to penicillin and 4% to ampicillin from the successfully treated group.

Gonorrhoea is the most commonly reported (80%) communicable disease in Jamaica, a Caribbean island with a predominantly black population of about 2·15 million.[1] An average of 26 240 cases of gonorrhoea was reported yearly in Jamaica during 1978–82, with a ratio of men to women of 3:1. The true incidence is estimated to be at least three times this figure. Adolescents and young adults are the primary targets, and 75% of infections occur in people aged 15 to 29. Those aged 20 to 24 are at greatest risk, having 33% of all reported infections and an incidence of 65 cases per thousand population.

Assessment of the susceptibility of strains of *Neisseria gonorrhoeae* to antimicrobial agents is essential if informed decisions are to be made about appropriate treatment. Treatment with an inappropriate antibiotic, or with an appropriate antibiotic in suboptimal doses, will not only fail to cure but will contribute to the selection of gonococcal mutants with decreased susceptibility to a given antimicrobial agent.[2] The emergence in other parts of the world of strains with plasmid mediated resistance to penicillin and tetracycline, as well as strains with high levels of chromosomally mediated resistance to penicillin, tetracycline, and spectinomycin, has underlined the necessity of screening gonococci for their susceptibility to antimicrobial agents.[2–9]

Two factors contributing to the emergence of penicillinase producing *N gonorrhoeae* (PPNG) isolates include suboptimal antibiotic dosage (through self medication) and population movement.[2 6] The former contributed to the emergence and maintenance of PPNG strains in areas such as the Phillipines and Singapore, the latter to the importation of strains into a variety of countries.[10–12] Jamaica is vulnerable to both of these factors; self treatment of gonorrhoea

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by buying antibiotics on the black market appears to be increasing in Jamaica in recent years (A Brathwaite, personal communication), and the national campaign to encourage tourism carries with it the possibility of importing PPNG strains which, up to 1983 when the present study was initiated, had not been isolated on the island.

The present study was undertaken to assess the prevalence of PPNG strains on the island, to compare the efficacy of aqueous procaine penicillin G with that of ampicillin in treating acute uncomplicated gonorrhoea, to estimate the minimum inhibitory concentrations (MICs) of eight antimicrobial agents for the *N gonorrhoeae* strains isolated during the study, and to correlate the susceptibility to antimicrobials with the efficacy of treatment.

Patients and methods

CLINICAL STUDIES

The study population comprised 1400 patients (515 men, 885 women) aged over 14 who visited the Comprehensive Health Centre, Kingston, Jamaica, for suspected gonorrhoea in June 1983 to April 1984. People were excluded from the study if they were minors (aged 14 or under), pregnant, allergic to the proposed drug regimens, infected with coexisting syphilis, known prostitutes, or had been treated with antibiotics or other drugs (such as corticosteroids or immunosuppressives) within the preceding 14 days. Patients were requested to abstain from sexual intercourse and to avoid all other medication pending evaluation after treatment.

Before treatment, urethral or endocervical swabs were inoculated on to modified Thayer Martin medium,[13] and were forwarded to the Microbiology Laboratory, University of the West Indies, where they were incubated for 48 hours at 35°C in a humid environment containing 5–10% carbon dioxide. Gram stained smears were immediately examined by direct microscopy at the Comprehensive Health Centre. Men were treated immediately on the basis of a positive smear. Women were asked to return within three days for the results of culture.

Men with positive Gram stained smears and women who had culture proved gonorrhoea on initial screening were allocated randomly to one of the following drug regimens: aqueous procaine penicillin G 4·8 MIU given in two intramuscular injection sites, or ampicillin 3·5 g orally. Each antibiotic was given with 1 g of probenecid orally. Patients were asked to return to the clinic for reassessment within three to seven days. At follow up urethral, endocervical, or rectal swabs (from women who failed to respond to treatment) were taken for test of cure cultures. Patients with evidence of gonorrhoea at follow up, as diagnosed by Gram stain and culture, were treated with spectinomycin 2 g, followed by a further test of cure three to seven days later. These patients were regarded as treatment failures.

IDENTIFICATION AND STORAGE OF ISOLATES

Isolates of *N gonorrhoeae* were initially identified by Gram staining, oxidase testing, and colonial morphology after 48 hours growth on modified Thayer Martin medium.[13] To purify the isolates, five to 10 typical colonies were subcultured on antibiotic free GC medium base (Difco Laboratories, Detroit, Michigan, USA) supplemented with 1% Kellogg's defined supplement, and incubated for 18 to 24 hours in a humid environment supplemented with 5–10% carbon dioxide at 36°C.[14] Isolates were also tested for the production of penicillinase using the chromogenic cephalosporin (Cefinase discs; BBL Microbiology Systems, Cockeysville, Maryland, USA) method.[15] Suspensions of these cultures were prepared in trypticase soy broth (Difco) supplemented with 15% glycerol, and were frozen at −70°C.[14]

Five hundred and five strains were forwarded to the Antimicrobials and Molecular Biology Division, Laboratory Centre for Disease Control, Ottawa, Canada, for confirmation of identity, reference antimicrobial susceptibility testing, and for biological, serological, and genetic characterisation (results of genetic and serological testing will be reported in a subsequent paper). Confirmation of the identity of the isolates was by carbohydrate utilisation, serology, and other standard tests.[16]

ANTIMICROBIAL SUSCEPTIBILITY TESTING

The MICs of eight antimicrobial agents for the isolates was estimated either immediately after primary isolation or, in most cases, after storage at −70°C. The MICs of penicillin, ampicillin, erythromycin, tetracycline, trimethoprim-sulphamethoxazole (at a ratio of 1:19) (United States Pharmacopial, Maryland, USA), spectinomycin (Upjohn, Toronto, Ontario, Canada), cefuroxime (Glaxo, Toronto) and thiamphenicol (Inpharzam, SA, International Pharmaceuticals, Zambon, Switzerland) were estimated using an agar dilution technique.[14] Reference strains WHO III, WHO V, and WHO VIII and the PPNG strain GC1-182 (from JR Dillon) were included as controls.[14,17] For testing MICs of sulphamethoxazole-trimethoprim diagnostic sensitivity test agar (DST agar; Oxoid, Basingstoke, England) supplemented with 5% lysed horse blood and 1% Kellogg's defined supplement was used. GC medium base supplemented with 1% IsoVitalex (BBL Microbiology Systems, Becton Dickinson, Cockeysville MD 2130) was used when testing the other seven antibiotics. The inoculum was prepared by

standardisation against a 0·5 McFarland opacity standard followed by a 1:100 dilution in 0·7% casamino acids[14] and subsequent inoculation with a Steers replicator on to medium containing antibiotic.[17] The plates were incubated as described previously for 18 to 24 hours. The MIC was considered to be the concentration of antibiotic either inhibiting all growth or allowing the growth of only one colony.

STATISTICAL ANALYSIS

Only patients with culture proved gonorrhoea who returned three to seven days after treatment were included in the analysis of success or failure of the two treatment regimens. The χ^2 test was used to analyse the difference in failure rates between the two regimens.

Results

TREATMENT

Of 1400 patients screened initially, 753 (54%) had uncomplicated gonorrhoea proved by culture and 27 of these patients were excluded from treatment for reasons cited in the Methods section. Of the 726 remaining patients who were treated with one of the two treatment regimens, 459 (63%) returned for follow up within seven days. In patients returning within seven days, 97% (211/218) of those treated with penicillin were cured compared with 94% (227/241) of those treated with ampicillin (χ^2 1·2; $p > 0·1$). More men treated with penicillin were cured (98%; 125/128) than those treated with ampicillin (91%; 126/139); χ^2 4·69; $p < 0·05$). Of women treated with penicillin, 96% (86/90) were cured compared with 99% (101/102) of those treated with ampicillin (χ^2 1·6; $p > 0·1$). Of patients returning for follow up test of cure within seven days, 14 were infected with PPNG strains. All of these patients were men, and PPNG isolates were the cause of 10 treatment failures (two patients treated with penicillin, and eight patients treated with ampicillin). If patients with PPNG infections are excluded from the analysis, the cure rate for men was 99% of those treated with penicillin and 96% of those treated with ampicillin, with no significant differences in results between drug regimens or between sexes.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

N gonorrhoeae was isolated from 753 of the 1400 patients screened, and 22 (3%) of these isolates produced β lactamase. MICs of eight antimicrobial agents were estimated for 629 non-PPNG strains (table 1). If resistance to penicillin, ampicillin, cefuroxime, and erythromycin is arbitrarily defined as an MIC of 1 mg/l or more, then 7% of the non-PPNG isolates were resistant to penicillin, 11% were resistant to ampicillin, and under 1% were resistant to cefuroxime and erythromycin. MICs of 2 mg/l or more of tetracycline were found in 12% of the strains. All isolates were inhibited by clinically achievable concentrations of spectinomycin and fewer than 2% of the isolates were resistant to thiamphenicol (MIC 2 mg/l or more).[18] Each isolate was susceptible to sulphonamides. Brown *et al* have reported that treatment with trimethoprim-sulphamethoxazole (TMP/SMX) is more likely to fail with MICs of 0·5 mg/l or more TMP and 9·5 mg/l or more SMX.[19] In this study all isolates were inhibited by these concentrations. The median MICs of the antimicrobial agents were, in descending order: cefuroxime 0·032 mg/l, penicillin 0·056 mg/l, erythromycin 0·05 mg/l, ampicillin 0·157 mg/l, thiamphenicol 0·206 mg/l, tetracycline 0·708 mg/l, sulphamethoxazole-trimethoprim (19:1) 1·1:0·06 mg/l, and spectinomycin 10·8 mg/l.

We recovered 22 primary PPNG isolates during the study. Not all the patients infected with PPNG strains could be included in the final analysis of treatment success, as eight of the 22 did not return to the clinic for test of cure. One of these patients was a woman. MICs were estimated for 20 strains (table 2). As might be expected, all PPNG strains were resistant to peni-

Table 1 *Minimum inhibitory concentrations of eight antimicrobial agents for 629 non-PPNG isolates*

	Cumulative % of strains inhibited by concentration (mg/l) of:										
Antimicrobial	*0·032*	*0·063*	*0·125*	*0·25*	*0·5*	*1*	*2*	*4*	*8*	*16*	*32*
Penicillin	29	58	73	84	91	92	97	99	100		
Ampicillin	12	21	40	74	86	89	96	100			
Cefuroxime	57	72	85	92	94	100					
Erythromycin	32	54	80	90	95	99	100				
Tetracycline		4	7	14	35	68	88	92	100		
Spectinomycin*								4	37	96	100
Thiamphenicol			18	61	76	87	98	100			
TMP-SMX† (1:19)	33	49	71	99	100						

*626 strains tested with spectinomycin.
†TMP-SMX, trimethoprim-sulphamethoxazole (1:19). Only trimethoprim concentration indicated (concentration of 0·032 implies trimethoprim 0·032 mg/l, sulphamethoxazole 0·64 mg/l).

Table 2 *Minimum inhibitory concentrations (MICs) of eight antimicrobial agents for 20 PPNG isolates*

Antimicrobial	MICs (mg/l) for: 50% strains	90% strains	Range
Penicillin	32·0	64·0	2·0 –64·0
Cefuroxime	0·125	2·0	0·016– 2·0
Erythromycin	0·25	1·0	0·032– 2·0
Tetracycline	1·0	2·0	0·25 – 4·0
Spectinomycin*	8·0	8·0	8·0 –16·0
Thiamphenicol	0·5	2·0	0·125– 4·0
TMP:SMX (1:19)†	16·0	32·0	0·5 –32·0

*17 strains tested with spectinomycin.
†See footnote of table 1.

Table 3 *Comparative susceptibility to penicillin and ampicillin of gonococcal strains from Jamaica (1971–84)*

Antibiotic	Year isolated*	No (%) of strains with MICs (mg/l) of†: ⩽ 0·03	⩾ 0·25	⩾ 1·0
Penicillin	1971	4(15)	10(39)	n/a
	1978	19(17)	10 (9)	n/a
	1983–4	179(29)	99(16)	47 (8)
Ampicillin	1971	3(12)	2 (8)	n/a
	1978	13(12)	2 (2)	n/a
	1983–4	78(12)	161(26)	68 (11)
Tetracycline	1971	n/a	19(73)	8(31)
	1978	n/a	61(54)	4 (4)
	1983–4	0	540(86)	199(32)

*26 strains tested in 1971,[22 23] 113 strains tested in 1978,[23] and 629 strains tested in 1983–4, present study.
†These MICs are comparative and do not denote levels of resistance.
n/a, not applicable.

cillin and ampicillin and over half had MICs of 32 mg/l or more. PPNG strains were generally more resistant than non-PPNG strains to antimicrobial agents, as indicated by the MIC_{50} (MIC inhibiting 50% of the isolates).

Of the 459 patients who returned for test of cure within seven days, 427 (including 21 treatment failures) yielded strains that were available for MIC testing. Of the 21 strains from treatment failures, 11 (52%) had MICs of penicillin of 1 mg/l or more compared with only 29 (7%) of the 406 strains from the successfully treated patients, a significant difference (χ^2 48·13; $p < 0·01$). Of the 21 strains from the treatment failures, 13 (62%) were shown to have MICs of ampicillin of 1 mg/l or more compared with 4% (46/406) of successfully treated patients (χ^2 42·89; $p < 0·01$). Ten (48%) of the *N gonorrhoeae* strains from patients who failed to respond to either treatment regimen were also penicillinase positive.

Discussion

Few studies have been undertaken to estimate the antimicrobial susceptibility patterns of gonococci isolated in the Caribbean area,[20 21] and no evaluations have been published about the outcome of treatment in the area. Statistical data on the incidence of gonorrhoea including cases caused by PPNG strains may be reported to the Pan American Health Organisation (PAHO), but the true magnitude of the problem is difficult to assess.[20] Two previous studies have estimated the susceptibility of strains of *N gonorrhoeae* isolated in Jamaica to antimicrobial agents.[22 23] Table 3 compares the results of these previous studies (undertaken in 1971 and 1978)[23] with those of the present study (undertaken in 1983–4); significant differences in levels of resistance were observed between each test period. Strains with MICs of 0·25 mg/l or more penicillin were observed in 38% of the 1971 isolates and in only 9% of the 1978 isolates (χ^2 15·34; $p < 0·001$). In the present 1983–4 study the proportion of strains with MICs of 0·25 mg/l or more increased to 16% compared with the 1978 results, but decreased in comparison with the 1971 results. These differences were not significant. The percentage of isolates resistant to this concentration of ampicillin showed an even greater increase, from 2% in 1978 to 26% in 1983–4 ($\chi^2 = 31·72$; $p < 0·01$). Similarly, MICs of tetracycline in the present study resembled the distribution observed in 1971, as opposed to observations in 1978.

Interestingly, in the present study the MIC_{90} of erythromycin (0·5 mg/l) and tetracycline (4 mg/l) compared with resistance levels reported by Rodriguez *et al* in Puerto Rico.[21] The median MICs observed in the present study, however, were lower than those observed in the Puerto Rican study. It would be interesting to ascertain whether tetracycline resistant gonococci were generally distributed throughout the Caribbean area. Several studies have established that treatment failure rates of at least 20% can be expected in strains with MICs of tetracycline of 1·0 mg/l or more.[24 25] The in vitro susceptibility estimates in the present study, in which 12% of the non-PPNG strains had an MIC of 2 mg/l or more, indicated that tetracycline alone would not be an optimum treatment regimen for gonococcal infections in Jamaica.

The susceptibility of non-PPNG strains to penicillin varies widely according to geographical source.[10 12] Sng *et al* reported that countries in South East Asia generally had the highest percentage of strains with reduced susceptibility to penicillin (MIC 0·5 mg/l or more),[10] whereas developed countries, except Japan[10] and Canada,[26] generally had a larger number (more than 80%) of susceptible strains. It should be pointed out that the report of Sng *et al* did not exclude PPNG strains,[10] and the high incidence of penicillin resistant isolates observed in South East

Asia reflected the high incidence of PPNG strains in those areas. In the present study, 9% of non-PPNG strains isolated in Jamaica had MICs of penicillin of 0·5 mg/l or more. This means that the susceptibility to penicillin of the Jamaican non-PPNG strains is similar to that of countries with a less than 5% incidence of PPNG strains. Most Jamaican gonococcal strains tested in this study were therefore susceptible to penicillin and ampicillin, a general characteristic of gonococcal isolates in Canada, most areas of the United States of America, and other countries where PPNG strains do not predominate. The overall sensitivity of the isolates to penicillin was reflected in treatment results showing that 97% of patients treated with penicillin were cured. Regimens with less than 95% cure rates are associated with an increased prevalence of resistant organisms.[2]

The present study is the first to report the detection of PPNG strains in Jamaica. Although the prevalence was only 3% of the total number of gonococcal strains isolated, this was undoubtedly an underestimate. Statistics on the incidence of PPNG strains in other Carribean countries are sparse, although PPNG strains have been reported from Trinidad and Tobago to PAHO officials (F Zacarias, personal communication) and strains have been imported into Canada from Antigua, Barbados, the Bahamas, the Dominican Republic, the Virgin Islands, Martinique, and Grenada.[27] Sng *et al* attributed the high prevalence of resistant strains in Singapore to the dominant role of prostitutes in the transmission of disease and to the improper use and inadequate control of sales of antibiotics to prostitutes and their clients.[10] These factors may play a part in the spread of PPNG strains in Jamaica. It is also probable that tourism plays a more important part by importing PPNG and other gonococcal strains.

In the present study 21 patients infected with PPNG strains were men and only one was a woman. The presence of PPNG strains in men in 21 of 22 patients is somewhat anomalous, despite the fact that many underdeveloped countries report high ratios of men to women infected.[20] There may be several reasons for the skewed ratios of men to women in this study; women who were prostitutes and therefore at highest risk for infection with PPNG strains were screened out of the study. As women were screened before men (before January 1984), PPNG strains were possibly not introduced to the island before December 1983 or January 1984, a period coincident with the onset of the annual tourist season.

Monitoring both the prevalence of PPNG strains and the susceptibility of gonococcal isolates to antibiotics is essential to Jamaican public health practice. The appearance of PPNG strains at a 3% level in Jamaica in 1984, coupled with the increasing resistance to penicillin compared with the results of studies undertaken in 1978,[23] indicates an urgent need for careful monitoring of the incidence of antibiotic resistant strains throughout the island. In addition, the susceptibility to antibiotics of all gonococcal isolates should continue to be monitored to ascertain whether antibiotic treatment for gonorrhoea on this island continues to be effective.

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